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RECORD OF ORAL HEARING

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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*Ex parte* KEITH V. WOOD, MONIKA G. GRUBER,
YAO ZHUANG, and AILEEN PAGUIO

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Appeal 2008-3429
Application 09/645,706
Technology Center 1600

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Oral Hearing Held: August 13, 2008

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Before DONALD E. ADAMS, LORA M. GREEN, and JEFFREY N. FREDMAN, *Administrative Patent Judges.*

ON BEHALF OF THE APPELLANT:

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P R O C E E D I N G S

MS. BEAN: Calendar Number 15, Mrs. Embretson.

JUDGE ADAMS: Thank you.

MS. BEAN: You're welcome.

MS. EMBRETSON: Good morning.

JUDGE ADAMS: Good morning, Ms. Embretson. Take your time when you're ready. As you know, you'll have 20 minutes. We're familiar with the issue, and if you'd begin by spelling your name into the record, we'd appreciate it.

MS. EMBRETSON: Certainly. Janet, J A N E T, Embretson, E M B R E T S O N. I represent the Assignee of the present appeal, Promega (phonetic sp.) Corporation of Madison, Wisconsin. The oral hearing for the related appeal was heard on June 17th of this year and the decision was mailed on July 22nd.

JUDGE FREDMAN: Is this -- was that 2008-2164?

MS. EMBRETSON: Yes, correct.

JUDGE FREDMAN: Because it -- I don't -- did it say in the Brief that they were related? I didn't see that.

MS. EMBRETSON: At the time they were serially numbered, and yes, we did.

JUDGE FREDMAN: Okay, so -- okay.

MS. EMBRETSON: Because the language of the claims in the matters is different I have prepared remarks to address all four of the appeal rejections. Should more be amenable I'd like to address them in the following order: the 112 second paragraph, the section 103 rejections, and if time permits the enablement rejection.

Before addressing whether the rejections in the present appeal should be reversed, I'd like a very brief statement, under two minutes, about some

of the elements and processes affecting transcription translation particularly because it's pertinent to the disclosures cited against the claims under section 103. And, then a very brief summary of the invention highlighting molecules in Example 1.

Numerous genetic elements regulate transcription which in turn can alter protein expression and natural selection works on both transcription and translation. However, genetic elements in molecules involved in gene expression generally primarily affect one transcription or post transcription by pre-translation processes or translation. And, they can be categorized accordingly.

What Appellant recognized was after modifying genes to alter coding frequency and after subsequent alterations, there were a large number of sequences of undesirable sites that were still in the sequences; in particular, a large number of transcription factor binding sites. Example 1 of the specification is exemplary where a codon optimized parent click beetle gene had 100 mammalian transcription factor binding sequences. And, those sequences were subsequently identified and removed yet the resulting molecule still had 50 and they were newly introduced in mammalian transcription factor binding sites.

Those sites then were removed in a -- fashion to end up with a synthetic molecule that was devoid of eukaryotic transcription factor binding sites, polymerase addition sites and some other specific sites. And that resulted in a molecule that's very divergent from the parent molecule.

Now, of the reciting classes of regulatory sequences in the claims, mammalian transcription factor binding sites, polymerase sites, five prime --

non-coding regulatory sequences and splice sites they span more than one codon. So, to alter those sites, it has to occur in the context of other codons.

As Figure 2 in the specification illustrates, the changes that you'll see from I think the center molecule was the parent molecule and then they -- these were evolved differently.

The changes that you end up with they reflect codon optimization and removal of transcription factor binding sites as well as other sequences. With that I'm going to move on to the 112 second paragraph.

The claim sets by the definite requirements of section 112 second paragraph the language the Examiner has objections to are a reduced number of combination of mammalian transcription factor binding sequences in trans-splice polyadenylation sites and prokaryotic five prime non-coding regulatory sequences. Also, where the mammalian transcription factor binding sequences are present in a data base, a transcription factor binding sequences and no mammalian transcription factor binding sequences as argued in the briefs.

Appellant has provided evidence that those phrases, mammalian transcription factor binding sites, intron splice sites, polyadenylation sites and prokaryotic promoter sequences which are five prime non-coding regulatory sequences would be recognized because they're conventionally used in the art. Or alternatively, those phrases would be understood in view of Appellant's disclosure. And, for evidence in particular in some of the art that is cited against Appellant under section 103.

In particular, we provided specifics transcription factor binding sites, splice sites, polymerase sequences, prokaryotic promoter sequences at Pages

48, 49, 50 of the specification. These sequences all have properties that are testable and recognizable. And yet, further evidence of those terms are understood is that there were data bases and software that could be used to search for those.

JUDGE FREDMAN: You mean they were commercially available at the time prior to the invention?

MS. EMBRETSON: That's correct. The Examiner did raise some concerns about calculated number of the sites and the change in scope over time. And, as discussed in the Appeal Brief, at least prokaryotic promoter sequences, polymerase sites and splice sites are relatively conserved. And, while transcription factor binding sites are much more diverse, it's likely that any sequence therefore would have a large number of those potentially have a large number of those relative to the other sequences that are recited in the claims.

As we had argued, even if there are new ones found over time, the other ones are still, were still available, are still known to one of -- and the fact -- it's the fact that you identify them not necessarily that you remove them.

And, so our synthetic molecules are different and they could be recognized because we -- there's a reduction in a combination of transcription factor binding sites. It's intentional. There are numerous different transcription factor binding sites that were removed in at least some of which were ones that reduced by codon optimization. Therefore, we believe the claim satisfies the requirement in section 112 second paragraph.

With regard to the section 103 rejections the Examiner has applied six different references to support one of the rejections under section 103 and an additional document to support a second rejection under 103. It's our position the Examiner had not met her burden of establishing a prima facie case of obviousness.

First, each reference documents a solution to a problem. If the problem is just generally gene optimization why does each reference solve the problem in a different way.

JUDGE FREDMAN: But, essentially we're talking about obviousness now.

MS. EMBRETSON: Yeah.

JUDGE FREDMAN: So, when you go reference by reference I don't think that's the proper approach. The approach is to look at what the, you know, knowledge of the art was at the time --

MS. EMBRETSON: Um-hum.

JUDGE FREDMAN: -- and in this context we have -- the artisan knows that you want to reduce things that are going to interfere; right?

MS. EMBRETSON: Correct.

JUDGE FREDMAN: And, the essential showing is how much time you spend doing it. How much do you want to optimize. And, your claims require a certain amount of optimization three fold --

MS. EMBRETSON: Not in this case.

JUDGE FREDMAN: -- does this have any -- amount of reduction?

MS. EMBRETSON: There, there is not a numerical value separate from this. A reduction between there are two points of reference --

JUDGE FREDMAN: So, this is, so this is even less than the related case. So, we want to optimize to reduce the level at some point. I mean, why wouldn't it be obvious to -- I mean how -- why -- given that people have been optimizing for the same features, why wouldn't it be obvious to optimize these genes?

MS. EMBRETSON: Well, I would say if you combine all the references then is what the, what is obvious is doing every change that's accumulative. A number of all these documents. And, our claims do specify which changes affirmatively are to be made. While it is true you could probably pick and choose going through these documents to find transcription factor binding sites the references --

JUDGE FREDMAN: Well, you've already admitted that the art has data bases of transcription factor binding sites --

MS. EMBRETSON: That is --

JUDGE FREDMAN: -- so if you're following the art, the art is in -- you run it through the computer. You pick out all that the art at least knows about --

MS. EMBRETSON: Um-hum.

JUDGE FREDMAN: -- and you remove them all.

JUDGE ADAMS: To just add onto that, if we do follow the teachings of the references and we do compile everything that the references teach wherein they list a whole bunch of different sequences that we could modify. Would that compilation include all those sequences that you're trying to modify in your claim; for example, Claim 1.

MS. EMBRETSON: I think what we bring is that we teach a hierarchy of things that should be removed because of the observation that by replacing codons you -- before Appellant's disclosure you, you could inadvertently introduce numerous transcription factor binding sites.

JUDGE ADAMS: Um-hum.

MS. EMBRETSON: And, that isn't in the art. So, even though Sherf (phonetic sp.) on a limited basis discloses that in a wild type sequence they did alter it that doesn't get you to say well codon optimization was introducing in particular transcription factor binding sites and those are what needs to be removed.

JUDGE ADAMS: Agreed, but, I mean, okay, so I would understand that your argument would be well we say there's ones that are really, really important that you need to, to move out; you need to change. But, if the prior art teaches a whole list that includes those that you say are really important to change, and a person of ordinary skill would recognize well gee here's all these things that could cause problems let's change them all. And, they would include what you're claiming, where's the difference?

MS. EMBRETSON: This goes to something that was in the Reply Brief and when I read it I don't know if it was particularly clear. This is on Pages 13 to 14. And, I -- two references I guess I'll choose that are mentioned there is Pan and Sherf. Pan certainly could look to the art that was available before they optimized their gene. Sherf issued in 1997, but they chose not to alter transcription factor binding sites. They don't say, you know, that's what I'm going to alter for my gene.

So, if one looks back and says oh, I'm going to take everything that's known and I'm going to alter my gene if it was so obvious why didn't they do it. They, again, one of skill in the art who has the body of work before them, each and every one of these actually gives specific things to change. I guess that goes back to looking at them as a whole I that they can be easily integrated because they're each trying to solve something differently.

They didn't all choose to make the same changes, nor did they all choose to start doing all the changes that were in, in the art that came before or that was available to them before.

JUDGE GREEN: But, your argument is that if it was so obvious why didn't they do it, if we take that tact aren't we getting rid of obviousness?

MS. EMBRETSON: I don't think so. I mean I that's speaking to the facts in this case, but again I guess we can go to KSR one or two references, simple substitution that might make the question of that here. The Examiner apparently needs six or seven references to make her case or allegedly make her case.

JUDGE GREEN: But, the number of references isn't, I mean --

MS. EMBRETSON: Um-hum.

JUDGE GREEN: -- that's not determined if you go over three references you can no longer have obviousness. I mean that's not the state of the law.

MS. EMBRETSON: Um-hum. No, but I think that it does bear some weight why do you need so many? Why is it so obvious, and going back to if Pan being the last, I guess, document that evidences that they had available things before why didn't they change theirs.

You know, I understand that in a sense I'm arguing why didn't someone do something, but there must have been a reason. It goes back to what each document was trying to do was to solve whatever problem they had in front of them. And, if gene optimization is just accumulative, again, that isn't what we're -- I guess what is in our claims, but it puts the cumulative of every change needs to be made that's what each and every document builds on each other. That's -- I think that's not the case. And, we chose the set of sequences that's recited in the claims for a particular reason.

JUDGE FREDMAN: Well, part of the reason the Examiner had to pick these is the compact prosecution issue trying to pick up all these members in the Markush group. So, I think to some extent the Examiner was just picking additional references to be safe in case you deleted things.

MS. EMBRETSON: Um-hum.

JUDGE FREDMAN: So, I'm not sure the number even is meaningful in any way.

MS. EMBRETSON: Okay. Alright.

JUDGE FREDMAN: But, I think that the question that, that we're still asking is under KSR where we're combining known things -- I mean this would be like if you took a mousetrap and you added poison in the snapper, right. So, we're writing two different elements that are known to be beneficial. Here, we're removing two different elements that are known to be deleterious.

MS. EMBRETSON: Um-hum.

JUDGE FREDMAN: Why isn't that obvious?

MS. EMBRETSON: I would say that it wasn't recognized that you could actually -- if you are used to mammalian codons, how could they, you know, introduce mammalian transcription factor binding sites? I guess it goes back to natural selection that if things were selected for a particular manner to be used in mammalian cells, and there was a discussion that I didn't go over in the background about -- or the balance between the two that you're introducing things that are deleterious, but yet they were initially selected in the mammalian codons to probably not introduce transcription factor binding sites because that would have affected impact each and every gene in there.

So, by putting them, by replacing them it wouldn't have been recognized. It was -- that's surprising because they're, they're complicated. I think we'd in the earlier appeal and certainly in this Appeal Brief you look at Faisst and Meyer which had a 150, these are complicated sequences. They aren't, as I pointed out, they aren't as concerned and there's a large number of them so the fact that they could be introduced it's such a, you know, a large number I think it was surprising. I mean there were 50 new ones just after mammalian codon replacement. I mean after those were tried as I go back to Example 1, there were 100 just after putting in high use. This one now in codons. And, then 50 new ones were reintroduced, and that's why the process was --

JUDGE FREDMAN: But, here really I mean all you have to do is one actually in this claim, this Brief, you know.

MS. EMBRETSON: Oh, so it's a reduction. Well, there are two, two comparisons. One is a reduction and the combination of them between I'm

going to call it the wild type I think it's the second synthetic molecule. But, it's also then a combination that's removed between the second and the first. And, again these are relative points. And, but overall you still have to have over 25 percent are replaced of the codons, so --

JUDGE FREDMAN: Right. That's -- optimization could result in that.

MS. EMBRETSON: Pardon?

JUDGE FREDMAN: Codon, codon optimization would suggest that sometimes anyway.

MS. EMBRETSON: Oh, well certainly codon optimization can be 100 percent of the codons --

JUDGE FREDMAN: Right.

MS. EMBRETSON: -- could be, but the codons, again, in the language of the claims is that the codons which are replaced are to remove something affirmatively to remove something specific.

JUDGE FREDMAN: Yeah. Alright.

MS. EMBRETSON: So, so I would say you wouldn't reasonably expect that, you know, codons that were used to express mammalian genes would also be able to introduce transcription factor binding sites and again I just want to refer back to how complicated that some of those binding sites can be. And, then with regard to distinguishing the facts in KSR which was brought up in the Reply Brief, I still think that there's something to be said for that there's a combination of six or seven documents appear to be necessary to make the Examiner's case.

Our subject matter, I believe, synthetic nucleic molecules is some, you know, is something very different than a vehicle control pedal apparatus. And, we aren't just substituting one known element for another or applying a technique. And I think as the art shows, going back to the art, there's not a finite number of identifying solutions to gene optimization.

With regard to Cornelissen and a teaching away I think the language is clear with regard to changes that are not needed and the chances of introducing sequences. They, they teach them very few modifications in the codon region a coding region art necessary. A codon replacement with codons used more frequently is not needed to alleviate expression and the chance of introducing undesirable sequences is unlikely.

With regard to the decision in the other case, I believe Ward said that quoted that reference and said teach away from a claimed invention when it suggests the line of development flowing from the reference disclosure is unlikely to be productive. I think a corollary is that if a line of development other than that flowing from the reference is unlikely to be protected. As a -- and that's the result that's sought by Applicant so --

JUDGE ADAMS: What, what case law would that be?

MS. EMBRETSON: One second.

JUDGE ADAMS: I think the --

MS. EMBRETSON: Oh, the corollaries is --

JUDGE ADAMS: --one you cited from --

MS. EMBRETSON: I'm just saying that--

JUDGE ADAMS: -- the one you cited from the Board's previous opinion was Grasselli ; right?

MS. EMBRETSON: Yes, that's correct.

JUDGE ADAMS: So, in support of your corollary what case would you say?

MS. EMBRETSON: I don't have. I'm just saying that that could be a corollary --

JUDGE ADAMS: Could be, okay.

MS. EMBRETSON: -- is that if there's a strong teaching you don't have to do something. Why would one do that? That's a teaching away from doing it.

I have treated the two rejections under 103 globally having separated them. The other reference, again, we had -- references are individual but as a combination I don't believe they would at all. I believe PCT Publication provides anything other than is disclosure about recursive mutagenesis to obtain end result. And, if time permits I'll go on to the enablement rejection.

JUDGE ADAMS: You have two minutes.

MS. EMBRETSON: Okay. The basis for the Examiner's rejection is claim breadth. The claims are allegedly directed to any variant DNA in any reporter polypeptide and that the alleged -- there's an alleged non-routine nature of screening. First, as supported by the evidence of record, the recited classes of reported polypeptides are known to the art and in fact they actually have already been subjected to mutagenesis and have amino acid substitution. We've also provided evidence that screening large numbers of molecules is routine in nature. And, with regard to reciting classes -- cat gene, beta glucuronidase , bete galactosidase and luciferases . I may have

forgotten one. But, they are well known molecules. There are screen methods.

And so we respectfully request reversal of the rejections and I thank the Court for its time.

JUDGE ADAMS: Any questions? You have any questions?

Thank you.

MS. EMBRETSON: Thank you very much.

(Whereupon, the hearing concluded at 11:00 a.m. on August 13, 2008.)